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Controlling Johne's disease: vaccination is the way forward

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M. avium subspecies *paratuberculosis*, hereafter referred to as MAP, is a significant veterinary pathogen that causes Johne's disease in ruminants, including cattle, sheep, and goats. This chronic intestinal disease is distributed worldwide and exacts a heavy economic toll on animal producers. For example, the dairy industry incurs substantial economic losses due to reduced milk production, premature culling, and reduced slaughter value (Raizman et al., 2009). It takes years for clinical signs to appear in animals after initial infection. The bacterium is shed in high numbers in the feces during this clinical phase of disease. Transmission is by ingestion of the bacterium while grazing on pastures contaminated by this shedding process. Milk, passed from the infected dam to the daughter, has also been shown as a transmission route (Stabel, 2008). To best combat this chronic infection, vaccination has the promise to reduce economic losses and control Johne's disease. In the conception of this eBook for Frontiers in Cellular and Infection Microbiology, we solicited communications describing technologies and approaches to immunize animals against Johne's disease.

Among the first large-scale vaccine trials for Johne's disease began in the early 1990s using killed whole cells in oil injected into cattle (Kormendy, 1994; Wentink et al., 1994). Those trials showed vaccination was useful to reduce shedding of the bacteria in the feces, thus potentially reducing cow-to-calf transmission, but was ineffective at preventing infection. Since that time, experiments have evaluated extracts of the bacteria and live cells in all hosts including sheep, goats, deer, and cattle. Furthermore, the strain of MAP used has varied greatly in those studies. Then in 2007, an effort was made to standardize the challenge models used to test new vaccines for combating Johne's disease (Hines et al., 2007). The parameters outlined for the goat model in that article were used to test the best available live attenuated candidates (Hines et al., 2014) as described in this eBook compilation.

The genome sequence and re-sequence of MAP (Li et al., 2005; Wynne et al., 2010) has greatly expanded our knowledge about proteins predicted to be located in the mycobacterial envelope through annotation and bioinformatic analyses. Even now, most of what is known can be obtained only from annotation predictions and computer modeling algorithms that suggest protein locations within a cell (Yu et al., 2010). A perfect example of the power of genomics was demonstrated a few years later when libraries of transposon mutants and transcriptomic studies were reported by several groups working with MAP (Shin et al., 2006; Wu et al., 2006, 2007; Janagama et al., 2010). Furthermore, genomics provided an important resource

for targeted construction of live-attenuated vaccine (LAV) candidates, which is the focus of several articles in this eBook. It is noteworthy that despite a focus on LAV strategies, we do not discount efforts directed toward the development of other vaccine technologies such as subunit or vectored vaccines (Hoek et al., 2010; Faisal et al., 2013; Thakur et al., 2013). Although these technologies are still under development, they could provide effective vaccines in the future.

Live attenuated vaccine strains of MAP are thought to be the best approach for vaccination against Johne's disease. Although traditional inactivated and LAV candidates cannot satisfy the DIVA approach, they will completely stimulate both cell-mediated and humoral immune responses (Park et al., 2011; Faisal et al., 2013). Numerous studies have suggested the role of cell-mediated immunity to provide protective responses against MAP infection, as suggested before in both the murine (Ghosh et al., 2014; Settles et al., 2014) and bovine models (Stabel et al., 2011) of Johne's disease. A partial analysis of the generated immune responses following immunization with novel LAV candidates is reported in this eBook (Hines et al., 2014) as part of a large scale vaccine trial. Additional analyses on the T cell populations and specific antigens detected will be forthcoming (Bannantine et al., unpublished).

To summarize the contributions to this research topic, the opening article reviews efforts by the Johne's disease research community to test available LAV strains of MAP through a series of three gated trials (Bannantine et al., 2014b). This trial series has been a coordinated international, multi-institutional effort that spanned several years. Many new ideas and retrospective approaches have emerged from this unprecedented effort. These aspects have been captured in this research topic. Details surrounding the construction of the attenuated mutants are also included as well as a list of the lessons learned from this integrated study. The next two articles describe a knockout mutant of *relA* (Park et al., 2014) and a library of transposon mutants (Rathnaiah et al., 2014). Both approaches are useful for generating live attenuated strains. The next three articles (Bannantine et al., 2014a; Hines et al., 2014; Lamont et al., 2014) describe in detail the three phases of the vaccine project summarized in the opening article. The remaining articles highlight immunological evaluation of subunit vaccines (Gurung et al., 2014), production of subunit vaccines using heterologous hosts (Johnston et al., 2014) and finally, take a unique look at the importance of post-translational modifications for vaccine design, with a highlight on glycoproteins (Facciolo and Mutharia, 2014).

REFERENCES

- Bannantine, J. P., Everman, J. L., Rose, S. J., Babrak, L., Katani, R., Barletta, R. G., et al. (2014a). Evaluation of eight live attenuated vaccine candidates for protection against challenge with virulent *Mycobacterium avium* subspecies *paratuberculosis* in mice. *Front. Cell. Infect. Microbiol.* 4:88. doi: 10.3389/fcimb.2014.00088
- Bannantine, J. P., Hines, M. E. II, Bermudez, L. E., Talaat, A. M., Sreevatsan, S., Stabel, J. R., et al. (2014b). A rational framework for evaluating the next generation of vaccines against *Mycobacterium avium* subspecies *paratuberculosis*. *Front. Cell. Infect. Microbiol.* 4:126. doi: 10.3389/fcimb.2014.00126
- Facciolo, A., and Mutharia, L. M. (2014). Mycobacterial glycoproteins: a novel subset of vaccine candidates. *Front. Cell. Infect. Microbiol.* 4:133. doi: 10.3389/fcimb.2014.00133
- Faisal, S. M., Yan, F., Chen, T. T., Useh, N. M., Guo, S., Yan, W., et al. (2013). Evaluation of a Salmonella vectored vaccine expressing *Mycobacterium avium* subsp. *paratuberculosis* antigens against challenge in a goat model. *PLoS ONE* 8:e70171. doi: 10.1371/journal.pone.0070171
- Ghosh, P., Steinberg, H., and Talaat, A. M. (2014). Virulence and immunity orchestrated by the global gene regulator sigL in *Mycobacterium avium* subsp. *paratuberculosis*. *Infect. Immun.* 82, 3066–3075. doi: 10.1128/IAI.00001-14
- Gurung, R. B., Purdie, A. C., Whittington, R. J., and Begg, D. J. (2014). Cellular and humoral immune responses in sheep vaccinated with candidate antigens MAP2698c and MAP3567 from *Mycobacterium avium* subspecies *paratuberculosis*. *Front. Cell. Infect. Microbiol.* 4:93. doi: 10.3389/fcimb.2014.00093
- Hines, M. E. II, Stabel, J. R., Sweeney, R. W., Griffin, F., Talaat, A. M., Bakker, D., et al. (2007). Experimental challenge models for Johne's disease: a review and proposed international guidelines. *Vet. Microbiol.* 122, 197–222. doi: 10.1016/j.vetmic.2007.03.009
- Hines, M. E. II, Turnquist, S. E., Ilha, M. R. S., Rajeev, S., Jones, A. L., Whittington, L., et al. (2014). Evaluation of novel oral vaccine candidates and validation of a caprine model of Johne's disease. *Front. Cell. Infect. Microbiol.* 4:26. doi: 10.3389/fcimb.2014.00026
- Hoek, A., Rutten, V. P., van der Zee, R., Davies, C. J., and Koets, A. P. (2010). Epitopes of *Mycobacterium avium* ssp. *paratuberculosis* 70kDa heat-shock protein activate bovine helper T cells in outbred cattle. *Vaccine* 28, 5910–5919. doi: 10.1016/j.vaccine.2010.06.042
- Janagama, H. K., Lamont, E. A., George, S., Bannantine, J. P., Xu, W. W., Tu, Z. J., et al. (2010). Primary transcriptomes of *Mycobacterium avium* subsp. *paratuberculosis* reveal proprietary pathways in tissue and macrophages. *BMC Genomics* 11:561. doi: 10.1186/1471-2164-11-561
- Johnston, C. D., Bannantine, J. P., Govender, R., Endersen, L., Pletzer, D., Weingart, H., et al. (2014). Enhanced expression of codon optimized *Mycobacterium avium* subsp. *paratuberculosis* antigens in *Lactobacillus salivarius*. *Front. Cell. Infect. Microbiol.* 4:120. doi: 10.3389/fcimb.2014.00120
- Kormendy, B. (1994). The effect of vaccination on the prevalence of paratuberculosis in large dairy herds. *Vet. Microbiol.* 41, 117–125. doi: 10.1016/0378-1135(94)90141-4
- Lamont, E. A., Talaat, A. M., Coussens, P. M., Bannantine, J. P., Grohn, Y. T., Katani, R., et al. (2014). Screening of *Mycobacterium avium* subsp. *paratuberculosis* mutants for attenuation in a bovine monocyte-derived macrophage model. *Front. Cell. Infect. Microbiol.* 4:87. doi: 10.3389/fcimb.2014.00087
- Li, L., Bannantine, J. P., Zhang, Q., Amonsin, A., May, B. J., Alt, D., et al. (2005). The complete genome sequence of *Mycobacterium avium* subspecies *paratuberculosis*. *Proc. Natl. Acad. Sci. U.S.A.* 102, 12344–12349. doi: 10.1073/pnas.0505662102
- Park, K. T., Allen, A. J., Bannantine, J. P., Seo, K. S., Hamilton, M. J., Abdellrazeq, G. S., et al. (2011). Evaluation of two mutants of *Mycobacterium avium* subsp. *paratuberculosis* as candidates for a live attenuated vaccine for Johne's disease. *Vaccine* 29, 4709–4719. doi: 10.1016/j.vaccine.2011.04.090
- Park, K. T., Allen, A. J., Barrington, G. M., and Davis, W. C. (2014). Deletion of *relA* abrogates the capacity of *Mycobacterium avium* *paratuberculosis* to establish an infection in calves. *Front. Cell. Infect. Microbiol.* 4:64. doi: 10.3389/fcimb.2014.00064
- Raizman, E. A., Fetrow, J. P., and Wells, S. J. (2009). Loss of income from cows shedding *Mycobacterium avium* subspecies *paratuberculosis* prior to calving compared with cows not shedding the organism on two Minnesota dairy farms. *J. Dairy Sci.* 92, 4929–4936. doi: 10.3168/jds.2009-2133
- Rathnaiah, G., Lamont, E. A., Harris, N. B., Fenton, R. J., Zinniel, D. K., Liu, X., et al. (2014). Generation and screening of a comprehensive *Mycobacterium avium* subsp. *paratuberculosis* transposon mutant bank. *Front. Cell. Infect. Microbiol.* 4:144. doi: 10.3389/fcimb.2014.00144
- Settles, E. W., Kink, J. A., and Talaat, A. (2014). Attenuated strains of *Mycobacterium avium* subspecies *paratuberculosis* as vaccine candidates against Johne's disease. *Vaccine* 32, 2062–2069. doi: 10.1016/j.vaccine.2014.02.010
- Shin, S. J., Wu, C. W., Steinberg, H., and Talaat, A. M. (2006). Identification of novel virulence determinants in *Mycobacterium paratuberculosis* by screening a library of insertional mutants. *Infect. Immun.* 74, 3825–3833. doi: 10.1128/IAI.01742-05
- Stabel, J. R. (2008). Pasteurization of colostrum reduces the incidence of paratuberculosis in neonatal dairy calves. *J. Dairy Sci.* 91, 3600–3606. doi: 10.3168/jds.2008-1107
- Stabel, J. R., Waters, W. R., Bannantine, J. P., and Lyashchenko, K. (2011). Mediation of host immune responses after immunization of neonatal calves with a heat-killed *Mycobacterium avium* subsp. *paratuberculosis* vaccine. *Clin. Vaccine Immunol.* 18, 2079–2089. doi: 10.1128/DOI.05421-11
- Thakur, A., Aagaard, C., Stockmarr, A., Andersen, P., and Jungersen, G. (2013). Cell-mediated and humoral immune responses after immunization of calves with a recombinant multiantigenic *Mycobacterium avium* subsp. *paratuberculosis* subunit vaccine at different ages. *Clin. Vaccine Immunol.* 20, 551–558. doi: 10.1128/DOI.05574-11
- Wentink, G. H., Bongers, J. H., Zeeuwen, A. A., and Jaartveld, F. H. (1994). Incidence of paratuberculosis after vaccination against *M. paratuberculosis* in two infected dairy herds. *Zentralbl. Veterinarmed. B* 41, 517–522.
- Wu, C. W., Glasner, J., Collins, M., Naser, S., and Talaat, A. M. (2006). Whole-genome plasticity among *Mycobacterium avium* subspecies: insights from comparative genomic hybridizations. *J. Bacteriol.* 188, 711–723. doi: 10.1128/JB.188.2.711-723.2006
- Wu, C. W., Schmoller, S. K., Shin, S. J., and Talaat, A. M. (2007). Defining the stressome of *Mycobacterium avium* subsp. *paratuberculosis* in vitro and in naturally infected cows. *J. Bacteriol.* 189, 7877–7886. doi: 10.1128/JB.00780-07
- Wynne, J. W., Seemann, T., Bulach, D. M., Coutts, S. A., Talaat, A. M., and Michalski, W. P. (2010). Resequencing the *Mycobacterium avium* subsp. *paratuberculosis* K10 genome: improved annotation and revised genome sequence. *J. Bacteriol.* 192, 6319–6320. doi: 10.1128/JB.00972-10
- Yu, N. Y., Wagner, J. R., Laird, M. R., Melli, G., Rey, S., Lo, R., et al. (2010). PSORTb 3.0: improved protein subcellular localization prediction with refined localization subcategories and predictive capabilities for all prokaryotes. *Bioinformatics* 26, 1608–1615. doi: 10.1093/bioinformatics/btq249

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